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Effectiveness and Metabolic Complications After 96 Weeks of a Generic Fixed-Dose Combination of Stavudine, Lamivudine, and Nevirapine Among Antiretroviral-Naive Advanced HIV-Infected Patients in Thailand: A Prospective Study

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ABSTRACT

BACKGROUND: Generic fixed-dose combination (FDC) antiretroviral therapy (ART) has been widely used in resource-limited settings. Treatment based on these combinations provide low pill burden and are less expensive.

OBJECTIVE: The aim of this study was to determine the long-term effectiveness and metabolic complications of a generic FDC of stavudine (d4T)/lamivudine (3TC)/nevirapine (NVP), among ART-naive HIV-infected patients.

METHODS: A prospective study was conducted among patients who were initiated on d4T/3TC/NVP between November 2004 and March 2005. Plasma HIV-1 RNA, CD4 and alanine transaminase were assessed every 12 weeks. Fasting plasma glucose (FPG) and lipid profile were determined at 96 weeks. Adverse events and genotypic drug resistance were recorded. The primary outcome of interest was the proportion of patients who achieved plasma HIV-1 RNA <50 copies/mL after 96 weeks of ART and analyzed by intent-to-treat (ITT) and on-treatment (OT) populations.

RESULTS: There were 140 patients (mean [SD] age, 35.7 [7.6] years; male, 67.9%) enrolled in the study. Median (interquartile range [IQR]) baseline CD4 was 31 (14–79) cells/mm^3 and HIV-1 RNA count was 433,500 (169,000–750,000) copies/mL. At week 96, 87 patients (ITT, 62.1%; OT, 87.0%) achieved HIV-1 RNA <50 copies/mL. Median (IQR) CD4 at 96 weeks was 328 (229–450) cells/mm^3. The reasons for drug discontinuation were as follows: drug resistance (9.3%), lost to follow-up (9.3%), NVP-related rashes (7.9%), death (5.0%), d4T-related adverse events (3.6%), and transferred to another hospital (2.1%). At 96 weeks, 25 patients (28.7%) had low-density lipoprotein cholesterol (LDL-C) >130 mg/dL, 7 (8.0%) had LDL-C >160 mg/dL, 6 (6.9%) had triglycerides >400 mg/dL, and 2 (2.3%) had FPG >126 mg/dL. Eleven patients (12.6%) had a lactic acid level >2.5 mmol/L. Eight patients (9.2%) needed to take antihypertensive

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agents. Of 13 patients who developed virologic failure, 76.9% and 61.5% had M184V/I and Y181C/I mutations, respectively.

CONCLUSIONS: Initiation of this FDC of d4T/3TC/NVP in these ART-naive patients with advanced HIV infection and low baseline CD4 cell count was effective at 96 weeks of follow-up with regard to virologic and immunologic responses. However, long-term metabolic complications, particularly dyslipidemia, were common and should be closely monitored. (*Curr Ther Res Clin Exp.* 2008;69:90–100) © 2008 Excerpta Medica Inc.

KEY WORDS: HIV, effectiveness, metabolic, GPOvir-S, nevirapine.

INTRODUCTION

The public health approach to antiretroviral therapy (ART) scale-up in resource-limited situations aims to support the development of treatment programs that can reach as many patients as possible. One of the keys to this approach is standardization and simplification of treatment regimens. Currently, nonnucleoside reverse transcriptase inhibitor (NNRTI)-based highly active ART (HAART) is an optional recommended regimen as an initial therapy for treatment-naive HIV-infected patients.[1,2] In addition, current ART guidelines[1] for HIV infection in adults and adolescents in the resource-limited settings recommend using 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus 1 NNRTI as the first-line antiretroviral regimen.[3] Regimens based on these combinations are efficacious, low pill burden, less expensive, generic formulations, and are available as fixed-dose combinations (FDCs).[4] This can preserve the protease inhibitor (PI) for future options and delay patient exposure to some adverse events (AEs) associated with PI drugs. Two NNRTIs are currently available for clinical use in the treatment of HIV disease. Nevirapine and efavirenz have been associated with antiretroviral effectiveness.[3,5,6] A 48-week, randomized, open-label trial in 1216 ART-naive patients found that both drugs had similar antiviral effectiveness.[3] Treatment failure occurred in 96 of 220 patients (43.6%) assigned nevirapine QD, 169 of 387 (43.7%) assigned nevirapine BID, 151 of 400 (37.8%) assigned efavirenz, and 111 of 209 (53.1%) assigned nevirapine plus efavirenz. At week 48, there were no significant differences among the study groups in the proportions with plasma HIV-1 RNA concentrations <50 copies/mL or increases in CD4 cells.

Since 2002, the Thai Government Pharmaceutical Organization (GPO), Bangkok, Thailand, has produced an FDC (GPOvir-S®) of 30- or 40-mg stavudine (d4T), 150-mg lamivudine (3TC), and 200-mg nevirapine (NVP). This combination formula (d4T/3TC/NVP) is administered as 1 tablet BID and facilitates a drug supply procedure for the national ART program. A previous pilot study[7] of bioequivalence found that NVP concentrations were above the recommended minimum (>3100 ng/mL). In a cohort of 6861 adult patients who initiated treatment with d4T/3TC/NVP, analysis of results determined effectiveness and tolerability of generic FDC in preventing AIDS-related mortality in resource-limited settings.[8]

There are some potential limitations of NVP-based ART including AEs, low genetic barrier (single mutation can confer drug resistance), cross-resistance within this drug class, and prevalence of NRTI-resistant viral strains in ART-naive HIV-infected pa-

tients.[2] Skin rash is the most frequently observed AE (17%) associated with NVP. The risk of rash at any severity is greatest in the first 6 weeks.[9] d4T-Associated metabolic complications include lactic acidosis, dyslipidemia, morphological changes, and dysregulation of glucose metabolism.[10] Symptomatic lactic acidosis is a rare (0.5–1/100 patient-years) but life-threatening complication due to prolonged NRTI administration, particularly d4T. Peripheral polyneuropathy is primarily associated with d4T and didanosine dideoxyinosine.[2] It usually presents with a distal symmetrical distribution and sensorimotor paralysis.

FDC ART has an advantage in terms of lower number of pills and cost. In Thailand, the cost of this regimen is approximately US $40 per month. These advantages are major reasons for successful ART scale-up in Thailand. However, one major concern regarding the use of generic FDC ART in the developing countries is its effectiveness. A search of the Thai-language literature of MEDLINE using the term *GPO-vir* found a number of published studies[11–15] regarding short-term effectiveness in Thais. In a 24-week, open-label, single-arm trial by Anekthananon et al,[11] patients administered generic d4T/3TC/NVP had a mean (SD) increase in CD4 cell count of 96.5 (63.5) cells/mm^3 ($P < 0.001$ vs baseline). The study by Kiertiburanakul et al[12] found that in a median follow-up of 15 weeks, 49 of 90 patients (54%) administered d4T/3TC/NVP achieved the goal of HIV RNA <50 copies/mL or ≥50% increased in CD4 cell count. Tin et al[13] found that, in 83 ART-naive patients with HIV infection, CD4 counts increased by a median of 78 × 10^6 cells/L during the first 3 months of treatment. After 2 years of treatment, 39.5% of the patients attained median CD4 counts >200 × 10^6 cells/L. A retrospective cohort study[14] conducted in ART-naive HIV-infected patients initiated on d4T/3TC/NVP found that there was no difference between patients with CD4 cell count <50 cells/mm^3 and those with ≥50 cells/mm^3 in terms of tolerability and effectiveness. In a 48-week, open-label, combined prospective and retrospective study[15] involving 102 HIV-infected patients with baseline CD4 cell count <100 cells/mm^3, the median CD4 cell count increased to 191 cells/mm^3.

Nonetheless, the long-term data regarding effectiveness and metabolic complications of d4T/3TC/NVP among advanced HIV-infected patients with low CD4 are still limited. Therefore, we conducted a prospective study to determine long-term immunologic and virologic outcomes and long-term metabolic events of d4T/3TC/NVP in HIV-infected patients who had baseline CD4 cell counts <250 cells/mm^3.

PATIENTS AND METHODS

The institutional ethics committees of the Bamrasnaradura Infectious Diseases Institute and the Ministry of Public Health, Nonthaburi, Thailand, approved the study. All patients provided written informed consent prior to study enrollment.

STUDY DESIGN

A prospective study was conducted among ART-naive HIV-infected patients who were initiated on d4T/3TC/NVP between November 2004 and March 2005 at the Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health. Inclusion criteria were as follows: (1) HIV-infected individuals >15 years old; (2) naive to ART

prior to d4T/3TC/NVP; (3) baseline CD4 cell counts <250 cells/mm^3; (4) initiated with a d4T/3TC/NVP; and (5) willing to participate and sign informed consent. Exclusion criteria were: (1) baseline serum creatinine level >2.0 mg/mL; (2) baseline alanine aminotransferase (ALT) >5 times the upper limit of normal; and (3) pregnancy. All patients were administered a separate NVP 200 mg QD lead-in dose during the first 2 weeks, prior to escalation to 200 mg BID. The patients received d4T 40 mg BID if body weight was >60/kg. In the presence of toxicity, the offending drug was substituted with second-line drugs; efavirenz was substituted for NVP and zidovudine was substituted for d4T. All patients were visited every 6 weeks to monitor clinical response and AEs as standard of care in our institute. The final decision regarding whether the relevant AEs were associated with study drug administration was made by the attending investigator.

All patients were followed-up for a total of 96 weeks after initiation of d4T/3TC/NVP. CD4 cell count, plasma HIV-1 RNA, and ALT enzyme were assessed at baseline, and after 12, 24, 36, 48, 60, 72, 84, and 96 weeks of ART. Total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and fasting plasma glucose (FPG) were assessed after 96 weeks of ART. The primary outcome of interest was the proportion of patients who achieved plasma HIV-1 RNA <50 copies/mL after 96 weeks of ART analyzed by intent-to-treat (ITT) and on-treatment (OT) groups. The ITT population included enrolled patients who received ≥1 dose of ART. OT analysis included all patients who completed 96 weeks of ART. The secondary outcomes were as follows: (1) change from baseline in CD4 cell count after 96 weeks of ART; (2) incidences of NVP-associated AEs including skin rashes and hepatotoxicity; (3) incidence of d4T-associated symptomatic lactic acidosis that led to discontinuation of d4T and serum lactic acid level of patients who continued d4T after 96 weeks; (4) proportion of patients who developed abnormal FPG or serum lipid levels and needed to commence antihypertensive agents; and (5) genotypic drug-resistance pattern after virologic failure.

The severity of skin rashes was determined using the AIDS Clinical Trial Group toxicities scale[16] as follows: Level I, erythema; Level II, diffuse maculopapular rash or urticaria; Level III, rash with constitutional symptoms, angioedema, serum sickness-like reactions, or Stevens-Johnson syndrome; and Level IV, toxic epidermal necrolysis. The patients' compliance was assessed by pill count at each visit and self-report. Noncompliance was defined by missing doses of >80% in the previous 4 weeks. In the case of noncompliance, patients were educated to improve the adherence to treatment.

CD4 cell counts were measured by flow cytometry. All of the plasma samples were analyzed for HIV-1 RNA using reverse transcription-polymerase chain reaction (COBAS AMPLICOR HIV-1 monitor version 1.5, Roche Diagnostics GmbH, Mannheim, Germany), according to the manufacturer's instructions. HIV-1 RNA levels were expressed as copy number per mL of plasma, and the lower detection limit of the assay was 50 copies/mL. Plasma samples were separated from the cell fraction by centrifugation at 700*g* for 10 minutes and then frozen at –70°C until tested for HIV-1 RNA. *Virologic failure* was defined as either a rebound plasma HIV-1 RNA of >1000 copies/mL after having a previously undetectable value, or lack of achievement to <50 copies/mL at 24 weeks of ART. Genotypic resistance testing was performed after the patient was

documented to have virologic failure. HIV-1 RNA was extracted from plasma samples, using a viral extraction kit (QIAamp, Qiagen Inc., Chatsworth, California). A genotyping assay (TruGene HIV-1, Visible Genetics Inc., Toronto, Canada) was used in conjunction with an automated DNA sequencing system (OpenGene, Visible Genetics Inc.) to sequence the protease and reverse transcriptase (RT) regions of the HIV-1 complementary DNA.

Blood samples used to measure lactate were collected at rest ≥15 minutes prior to phlebotomy with no use of tourniquets and no fist clenching while blood was drawn. The samples were kept in fluoride tubes to prevent further lactate production and were rapidly delivered to the test laboratory on ice. Analysis was conducted using a bench-top analyzer (COBAS INTEGRA 400, Roche Diagnostics Corp., Indianapolis, Indiana).

STATISTICAL ANALYSES

Mean (SD), median (interquartile range), and frequencies (%) were used to describe patients' characteristics. The proportion of patients with plasma HIV-1 RNA <50 copies/mL after 96 weeks of ART were analyzed as ITT and OT populations. Missing data on plasma HIV-1 RNA levels were taken to be >50 copies/mL. Patients experiencing AEs, or anything that might have led to change, modification, or discontinuation of the regimen, were excluded from the final analysis at week 96. Cox regression analysis was used to determine risk ratio. Statistical calculations were performed using SPSS version 11.5 (SPSS Inc., Chicago, Illinois). A 2-sided $P < 0.05$ was considered statistically significant.

RESULTS

There were 140 patients (mean [SD] age, 35.7 [7.6] years; male, 67.9%) enrolled in the study. Baseline characteristics of the patients are shown in **Table I**. Six patients did not meet inclusion criteria. One hundred patients were still receiving treatment after 96 weeks of follow-up. At week 96, 87 patients (ITT, 62.1%; OT, 87.0%) achieved HIV-1 RNA <50 copies/mL. The percentage of patients who achieved undetectable plasma HIV-1 RNA <50 copies/mL and CD4 cell count response at each study time point are shown in **Figures 1** and **2**, respectively. At 12, 24, 36, 48, 60, 72, 84, and 96 weeks, median CD4 cell counts were 142, 182, 223, 234, 254, 321, 322, and 328 cells/mm^3, respectively. By Cox regression analysis, HIV-infected patients who had plasma HIV-1 RNA at 12 weeks ≥400 copies/mL were 17 times more likely to have virologic failure after 96 weeks of ART ($P = 0.001$), as shown in **Table II**.

The reasons for drug discontinuation were as follows: drug resistance (13 patients [9.3%]); lost to follow-up (13 [9.3%]); NVP-related skin rashes, grades II and III (11 [7.9%]); death (7 [5.0%]); d4T-related neuropathy (4 [2.9%]); transferred to another hospital (3 [2.1%]); and symptomatic lactic acidosis (2 [1.4%]). All NVP-related skin rashes developed within the first 12 weeks after initiation of ART. At 12 weeks after ART, 5 of 121 patients (4.1%) developed ALT >3 times the upper limit of normal. None of the patients developed clinical hepatitis. All causes of death were deemed not to be related to study drugs. During the study period, 30 patients (21.4%) in this cohort needed to change to other regimens.

Table I. Baseline demographic and clinical characteristics of antiretroviral therapy-naive HIV-infected patients in Thailand (N = 140).

Characteristic	Value
Age, mean (SD), y	35.7 (7.6)
Male sex, no. (%)	95 (67.9)
Weight, mean (SD), kg	54.2 (9.7)
CD4 cell count, median (IQR), cells/mm^3	31 (14–79)
CD4 percentage, median (IQR)	4 (2–6)
Plasma HIV RNA, median (IQR), copies/mL	433,500 (169,000–750,000)
Alkaline phosphatase, median (IQR), U/l	98.0 (71.0–142.5)
Alanine transaminase, median (IQR), U/l	30.0 (20.0–50.0)
Total bilirubin, median (IQR), mg/dL	0.56 (0.43–0.73)

IQR = interquartile range.

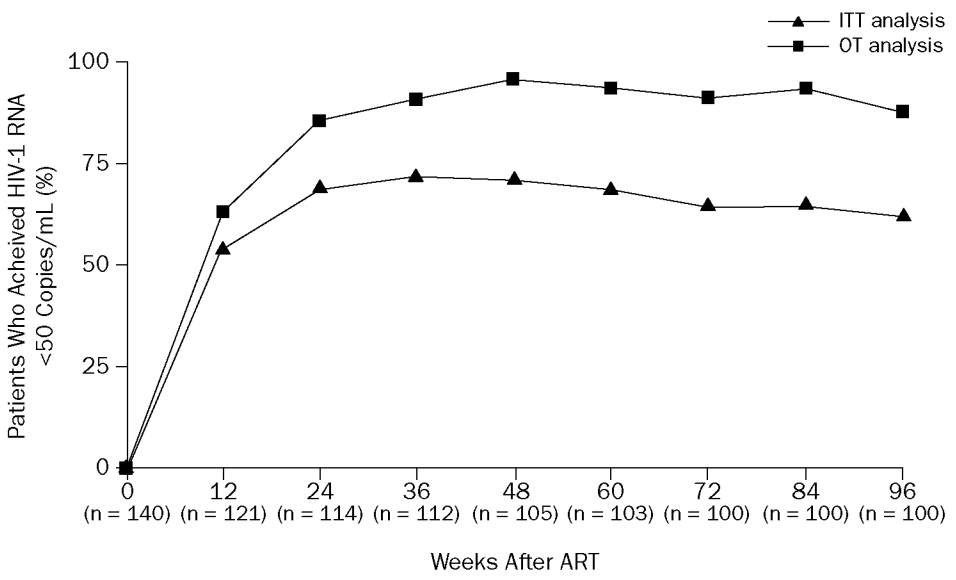

Figure 1. Percentage of antiretroviral therapy (ART)-naive advanced HIV-infected patients (both intent-to-treat [ITT] and on-treatment [OT] populations) in Thailand who achieved undetectable plasma HIV-1 RNA <50 copies/mL after administration of a generic fixed-dose combination of stavudine, lamivudine, and nevirapine for 96 weeks.

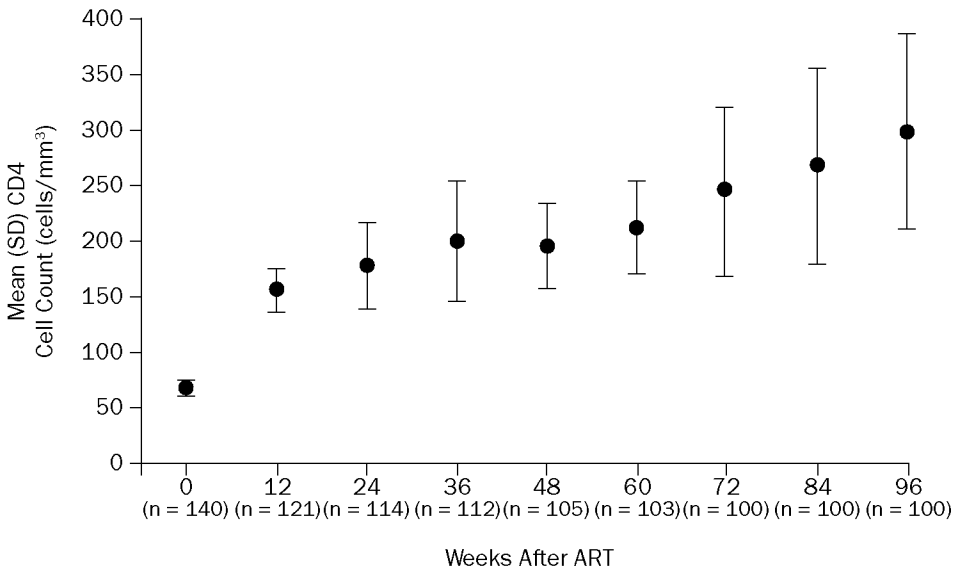

Figure 2. Immunologic outcomes after 96 weeks of antiretroviral therapy (ART) with a generic fixed-dose combination of stavudine, lamivudine, and nevirapine in ART-naive advanced HIV-infected patients in Thailand.

At 96 weeks, 54 patients (62.1%) had total cholesterol >200 mg/dL, 25 (28.7%) had LDL-C >130 mg/dL, 7 (8.0%) had LDL-C >160 mg/dL, 6 (6.9%) had triglycerides >400 mg/dL, and 2 (2.3%) had FPG >126 mg/dL, respectively. Eleven patients (12.6%) had lactic acid levels >2.5 mmol/L; all 11 were asymptomatic hyperlactatemia. Eight patients (9.2%) needed to commence antihypertensives. No risk factor was found to be associated with total cholesterol >200 mg/dL after adjusting for age, sex, and baseline weight.

Table II. Cox regression of possible risk factors for achieving undetectable plasma HIV-RNA <50 copies/mL after 96 weeks of antiretroviral therapy in ART-naive HIV-infected patients in Thailand (N = 140).

Risk Factor	HR	95% CI	*P*
Plasma HIV-RNA ≥400 copies/mL at 12 weeks	17.241	3.067–100.000	0.001
Age	0.961	0.878–1.052	0.389
Sex	1.024	0.229–4.580	0.976
Weight	1.015	0.937–1.099	0.720
Baseline CD4 cell counts	1.006	0.994–1.019	0.312
Baseline log plasma HIV-RNA	1.775	0.466–6.757	0.400

HR = hazard ratio.

Among the 13 patients with drug resistance, 5 (38.5%) had mutations contributing to NRTI resistance, 1 (7.7%) had NNRTI resistance, and 7 (53.8%) had both NRTI and NNRTI resistance. Of the NRTI-resistant mutations, M184V/I was the most common (10 [76.9%]). Thymidine analog–associated mutations (TAMs) were found in 1 patient (7.7%). K65R was observed in 2 patients (15.4%). For NNRTI-resistant mutations, there were Y181C/I (8 [61.5%]) and K103N (1 [7.7%]).

DISCUSSION

The results from the present study suggest that a generic FDC, d4T/3TC/NVP, had favorable long-term effectiveness for ≥96 weeks. Approximately 62% of patients achieved undetectable plasma HIV-1 RNA <50 copies/mL by ITT analysis. When compared with 65.4% (253/387) of patients who achieved undetectable plasma HIV-1 RNA at 48 weeks in a prospective comparative study,[3] the antiviral effectiveness of d4T/3TC/NVP appears satisfactory.

In the resource-limited countries, including Thailand, HIV-infected patients usually present late with very low CD4 cell counts.[17] Although a significant proportion of patients (75%) in the present study had baseline CD4 cell counts of <80 cells/mm^3, there was a marked increase of CD4 cells after 96 weeks. The increment was not blunted by the very low baseline CD4 cell counts. Overall, the virologic and immunologic effectiveness was consistant with that reported from ART in the developed countries.[3] The well-established predictors of long-term virologic success include potency of ART regimen, adherence to treatment, low baseline viremia, higher baseline CD4 cell counts, and rapid reduction of viremia in response to treatment.[18,19] In the present study, patients who still had plasma HIV-1 RNA levels at week 12 of >400 copies/mL were 17 times more likely to have diagnosed virologic failure by multivariate analysis. A prospective observational cohort study conducted in Barbados in 158 antiretroviral-naive HIV patients also demonstrated that there was a high rate of virologic and immunologic success (123 patients [78%] achieved viral loads of <50 copies/mL) after 6 months of HAART, irrespective of the pre-HAART viral load and CD4 cell count.[20] Therefore, baseline CD4 cell counts was not a predictive factor of virologic failure.

Regarding the short-term AEs, all were attributed to NVP. Despite receiving 2 weeks of NVP 200-mg QD lead-in dose prior to escalation to 200 mg BID, ~8% of patients had developed NVP-associated skin rashes (grade II–III) that led to NVP discontinuation. All of these patients tolerated efavirenz well. Previous studies[3,21] found that NVP may cause a mild skin rash in 15% to 20% of patients, 5% to 10% of whom discontinued treatment. This rate is similar to that observed in the previous studies in Thais.[11,22] Our recent study[23] reported 1.2-fold greater chance of developing NVP-associated skin rashes in every increment of baseline CD4 50 cell counts of cells/mm^3.

Long-term administration of NRTI, particularly d4T, can cause mitochondrial toxicity.[2] The clinical manifestations of this AE present as hyperlactatemia and polyneuropathy.[24] In the present study, d4T-related neuropathy and/or symptomatic lactic acidosis was observed in 4 (2.9%) and 2 (1.4%) patients, respectively, after 96 weeks of treatment. Although this number is relatively low, this well-established AE should be closely monitored in long-term treatment. In addition, prolonged administration of d4T

is associated with increased triglycerides and cholesterol.[2] Routine monitoring of lipid levels should be assessed among the patients who receive this drug.[2] Currently, d4T is not a first-line antiretroviral drug recommended in the recent developed country guidelines due to its significant toxicities.[25] The role of d4T as a preferred companion NRTI drug should be reconsidered in future revised treatment guidelines in the resource-limited settings including Thailand. NRTIs with less toxicity should be considered as substitutions for d4T in the core regimen.

Another concern is the emergence of drug resistance due to the low genetic barrier of NVP and 3TC in the regimen. The most common changes selected by NVP involve a K103N mutation and a Y181C/I mutation.[26] The present study found that almost all of NVP-associated mutation was Y181C/I. Eight percent had K103N while >60% had Y181C/I. Resistance to 3TC is conferred by a point mutation at RT codon 184, producing M184V or M184I.[27,28] Therefore, it is not surprising that ~77% of the patients had M184V/I. The options of a second-line regimen are still available for these patients, based on a low rate of TAMs; zidovudine plus didanosine and zidovudine plus tenofovir would be available options. In the present study, plasma HIV-1 RNA was assessed every 12 weeks through 96 weeks of ART. However, with regard to real-life clinical practice in resource-limited situations, plasma HIV-1 RNA might not be regularly performed every 12 weeks as in this study.

Our findings may support the prescribing of d4T/3TC/NVP to patients in resource-limited settings. However, d4T-associated long-term metabolic complications, particularly dyslipidemia and lactic acidosis, are common and should be closely monitored. Strategy to minimize long-term toxicity of d4T/3TC/NVP, such as switching to other ART combinations at an optimal time, should be evaluated.

LIMITATIONS

The study design was not comparative, which might have been essential to evaluating the effectiveness of an antiretroviral regimen. The study also was not blinded and AEs were not monitored. Though the sample size was relatively small, results of the present study may provide useful clinical data for the care of advanced HIV-infected patients in developing countries. Baseline hepatitis B, hepatitis C serology, baseline lipid profile, and FPG were not performed prior to ART initiation. Thus, the actual proportion of patients who developed metabolic complications may not be accurate. However, the high number of cases (4 d4T-related neuropathy and 2 symptomatic hyperlactatemia) in this study may reflect some degree of this complication. Lastly, lactate measurement was not repeatedly performed at each time point. However, we perform this laboratory test within the 15-minute rest period prior to phlebotomy, without the use of tourniquets and fist clenching. Therefore, we consider the lactate level from a single lactate measurement to be reliable.

CONCLUSIONS

Initiation of this FDC of d4T/3TC/NVP in these ART-naive patients with advanced HIV infection and low baseline CD4 cell count was effective at 96 weeks of follow-up with regard to virologic and immunologic responses. However, long-term meta-

bolic complications, particularly dyslipidemia, were common and should be closely monitored.

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